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**Short Communication**

# Alanine Increases Blood Pressure During Hypotension

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Many amino acids reportedly alter cardiovascular function when administered parenterally. The most studied such compound has been tyrosine, which increases blood pressure (BP) during haemorrhagic shock (Conlay *et al.* 1981), and decreases BP in spontaneously hypertensive rats (SHRs) (Sved *et al.* 1979). Tryptophan similarly reduces BP in SHRs (Sved *et al.* 1982); glycine increases cardiac output and decreases mean arterial pressure in dogs (Wang *et al.* 1985); and methionine reduces the contractile responses of the rat's aorta to potassium chloride (Landon *et al.* 1986). Butta & Adler-Graschinsky (1987) recently reported that low concentrations of L-alanine diminished norepinephrine release from the cardiac sympathetic nerves in isolated rat atria. In contrast, higher concentrations of the amino acid increased the contractile responses to exogenous norepinephrine (Butta & Adler-Graschinsky 1987), suggesting that L-alanine might also act *in vivo* to modulate cardiovascular responses to circulating catecholamines (Butta & Adler-Graschinsky 1987). Catecholamines mediate compensatory responses to haemorrhage, and since their physiologic effects could potentially be altered by L-alanine, we examined the amino acid's effects on BP during haemorrhagic shock.

Male Sprague-Dawley rats (retired Charles River breeders weighing approximately 500 g), were anaesthetized with chloralose and urethane (50 and 500 mg/kg intraperitoneally). Their left carotid arteries were cannulated for BP measurement, blood removal, and drug administration. Animals were bled through the cannula in 1 ml increments every 3 min. until their systolic BP reached approximately 50 mmHg. One hr later they were treated with L-alanine (1, 10, 25, 50, 100, or 200 mg/kg), pyruvate (100 mg/kg), or saline. All solutions were dissolved in saline, and administered through the cannula in volumes of 1 ml/kg. In order to estimate the increase in the plasma concentration of L-alanine following its intravenous administration, we assayed this amino acid in plasma samples obtained just prior to, and 15, 30, or 60 min. after administration of the 100 mg/kg dose. L-alanine was measured by high pressure liquid chromatography using a post-column derivative with orthophthaldehyde (Chan 1985). BP was recorded throughout the experimental period using a Grass Polygraph and Statham transducers. Data representing the peak change in the animals' systolic BP following drug administration were analyzed using analysis of variance.

L-alanine in doses of 10, 25, 50, 100, and 200 mg/kg significantly increased the systolic BP of hypotensive rats by 19–41 mmHg (38–88%, $P<0.05$, fig. 1). However, a 1 mg/kg dose did not increase BP more than a similar volume of saline. L-alanine's pressor action began approximately 1 min. following its administration, and persisted from 5 to 15 min., depending on the amino acid's dose. In contrast, pyruvate, 100 mg/kg, increased BP by only $9.4\pm4$ mmHg; thus its pressor activity did not differ significantly from saline ($7\pm3$ mmHg, $P>0.75$).

Plasma concentrations of L-alanine increased by approximately 14 fold (i.e., from 0.4 to 6.6 mM) 15 min. after intravenous administration of the 100 mg/kg dose. Levels declined rapidly thereafter, to 1.05 mM 1 hr after the amino acid had been administered.

While the mechanism of L-alanine's pressor activity is unclear, it could involve any of several processes. First, L-alanine, like α-(methylamino)-isobutyric acid, a direct-acting analogue, could have directly constricted smooth muscle cells located in arteriolar walls (Butta & Adler-Graschinsky 1987), and thus increased BP. Such an action is unlikely to represent a non-specific effect of amino acids on vascular contractility, since no increases in BP were observed after treatment with leucine, isoleucine, or tryptophan using a similar experimental paradigm (Conlay *et al.* 1981). Second, pyruvate, a degradation product of L-alanine, could have served as an energy source during haemorrhagic shock. However, this hypothesis is contradicted by the failure of exogenous pyruvate administration (100 mg/kg) to increase BP in our haemorrhaged-hypotensive animals. L-alanine's conversion to pyruvate is coupled with α-ketoglutarate's transamination to glutamate. Although glutamate serves as an intermediate for the excretion of the nitrogen derived from many amino acids, it could also conceivably exert physiologic effects. But in contrast to L-alanine (Butta & Alder-Graschinsky 1987), glutamate exerted no demonstrable effects on the isolated heart preparation (Pinto & Maher 1986). Third, L-alanine could have raised BP by increasing the sensitivity of α-receptors to endogenous norepinephrine, as also described by Butta & Adler-Graschinsky (1987) for concentrations approximating 1 μM *in vitro*.

L-Alanine's ability to modulate peripheral sympathetic neurotransmission (Butta & Adler-Graschinsky 1987) and to increase BP during hypotension (fig. 1) suggests that this circulating amino acid might influence cardiovascular

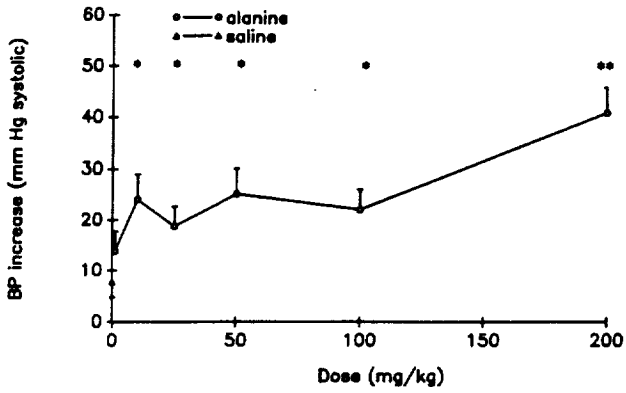


Fig. 1. Peak increase in systolic BP following the administration of L-alanine (1, 10, 25, 50, 100, or 200 mg/kg, n = 6,5,8,6,12 per group, respectively) or saline (n = 13) to animals that had previously been hypotensive for 1 hr. Data represent means ± S.E.M., $^{*}P < 0.05$, $^{**}P < 0.01$.

function. A water soluble dipeptide containing tyrosine and L-alanine has recently been shown to cause dose-related increases in BP in haemorrhaged-hypotensive rats (Maher *et al.*, unpublished results); conceivably the L-alanine released from this peptide might have participated in the pressor response.

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